Cengent Therapeutics Inc. (formerly Moldyn Inc.)

Enhanced Molecular Dynamics Simulation for Drug Research

In the field of drug discovery, molecular dynamics (MD) simulation is used to understand protein structure, small molecule and protein interactions, and protein and protein interactions. While several commercial software packages started offering enhanced molecular dynamics simulation capabilities in the 1990s, the time required for a realistic simulation was too long, partly due to the slow speed of the computers and partly due to the way the biological system is treated in such simulation, which is atom-based. A complete ("all-atom") model simulation could be ideal for understanding atom-to-atom interaction in drug discovery, but could be a major bottleneck if feedback is needed quickly for biologists and chemists in an software/researcher-integrated drug discovery environment.

Moldyn Inc. was founded in 1993 by Photon Research Associates to research a way to make MD simulation via software less expensive and time-consuming by simplifying the MD simulation process. Moldyn proposed to replace the all-atom molecular model with a model that used groups of atoms that behave similarly to specific individual atoms in a disease process. Drug research using simulation processes is extremely laborious, time-intensive, and expensive; moreover, it carries high technical risk for any company attempting the process. Therefore, because Moldyn's own capital resources were limited due to the project's high risk, in 1994 the company applied for and received a three-year Advanced Technology Program (ATP) award. The proposed project to research MD simulation software to aid in finding new drug substances began in 1995. Moldyn's goal for MD simulation was to model approximate groups of atoms in a molecule instead of modeling exact maps of all the atoms of a molecule. If a breakthrough using MD simulation could be made, new drug research candidates could be discovered faster and more economically. If successful, MD simulation would replace the trial-and-error techniques prevalent in the drug research industry with a more precise and targeted identification method.

After two years, Moldyn had succeeded in developing the software and benchmarked it with other existing molecular dynamics tools. Its performance was shown to be superior. Moldyn then chose Molecular Simulations, Inc., to further develop it for incorporation with a suitable Graphical User Interface (GUI) and commercialization. Since Molecular Simulations already had competing products, the company spent very little in implementing a GUI but started offering the software as an independent module. Molecular Simulations then became a subcontractor and licensee, but stopped upgrading and selling the product. Subsequently, Cengent Therapeutics Inc. bought Moldyn and abandoned the software, as the business plan of Cengent did not include software product offerings.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* *

Research and data for Status Report 94-01-0137 were collected during May – July 2004.

Molecular Dynamics (MD) Simulation Software Could Speed New Drug Development

According to the Pharmaceutical Research and Manufacturers of America, it takes between 10 and 15 years and more than $800 million to bring a new drug to the U.S. market. This significant investment of time and money is due to the large number of target substances available for researchers to select from, as well as the

complexity of the research that is needed on these substances.

Molecular dynamics (MD) simulation is used to study the interactions between drug molecules and the active sites on a receptor protein. In drug research, a receptor protein is an organic molecule that needs to be altered to interrupt a disease process. The receptor molecule receives the drug target molecule at the “active site,” located somewhere on the molecule. The target drug blocks the active site from further interaction with other proteins and stops the disease process, arresting the process at the molecular level. These target drugs must be extensively tested to ensure that they will bind with efficacy and selectivity at the active site on the receptor protein.

In the early 1990s, several commercial software packages offering MD simulation were available to help researchers study likely candidates for drug research, but these packages used all-atom molecular models. This meant that an entire molecule, such as a receptor protein, was modeled atom-by-atom by the software program until a complete mathematical model of the molecule was built (on the computer). The model was constructed according to three-dimensional coordinates for each atom in the molecule, which were entered by the user into the software program. Then candidate drug molecules were inserted near the active sites on the molecule to start the dynamics simulation. If the drug bound to the active site of the molecule, the drug was a candidate for more research.

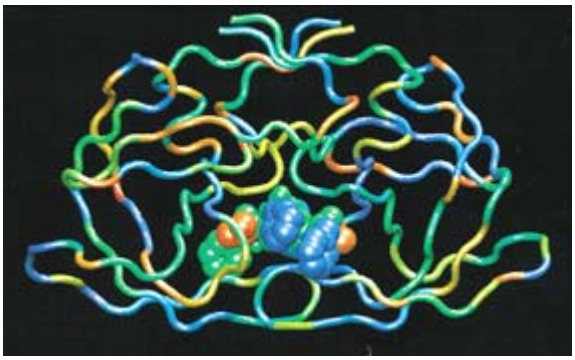

Figure 1. Example of a software-generated model of a drug/protein molecular interaction. This model represents 100,000 or more atoms.

There are thousands of proteins in the human body, and a protein molecule can consist of thousands of atoms. Therefore, many variables in the software must be controlled to ensure that the correct active site, which consists of atoms in a region of a molecule, gets targeted. Using software to model a large molecule consisting of 100,000 or more atoms could take months (see Figure 1).

Moldyn Proposes to Improve MD Simulation with Substructuring

To reduce the time required to model a molecule and to find its active sites, Moldyn, a company founded in 1993 by Photon Research Associates, wanted to modify the existing molecular modeling software. Moldyn initially received two Federal grants that they used to demonstrate the feasibility of MD simulation technology based on the generation of molecular clusters called “bodies”. Then, in 1994, the company applied for and received a three-year ATP award to research ways to enhance the molecule-modeling software that was available at the time. Starting the research in 1995, the company attempted a breakthrough approach by modeling approximate groups of atoms in a molecule as flexible and rigid bodies instead of modeling all the molecule’s atoms individually. Because Moldyn’s MD simulation model assumes that approximate groups of atoms behave similarly to individual atoms, an atom group, called a substructure, could substitute for several exact maps of individual atoms in appropriate parts of the protein. If Moldyn’s software enhancement was successful, molecules and drug interactions with molecules could be modeled more quickly, and new drug development candidates could be isolated faster, thus saving time and money.

Substructuring Poses Significant Technical Challenges

The implementation of Moldyn’s proposed enhancements to the MD simulation software was formidable. The company wanted to modify a method that mapped the three-dimensional coordinates of every atom in a molecule. Molecules could consist of 100,000 atoms or more, so the software user must possess extensive knowledge regarding which nonactive substructures could have their degrees-of-freedom reduced without sacrificing accuracy in modeling the interaction of drug molecules to receptor protein active sites. Degrees-of-freedom are the atomic or molecular dynamic motions that move up, down, and across in a three-dimensional environment. The motions are related to the three-dimensional coordinates of each atom in a molecule. The Moldyn researchers sought to represent more efficiently the degrees-of-freedom of

molecules. Software similar to Moldyn's proposed technology was already being used in the aerospace industry to predict spacecraft movements in zero gravity environments.

Substructures in Moldyn's MD method can bend, twist, and fold, so that the resulting dynamic model of the molecule can have bends, twists, and folds just as would be realized in a traditional all-atom simulation. These dynamic degrees-of-freedom were an important variable, because reducing the degrees-of-freedom in regions of the protein that were unimportant to the dynamic motions of the active site was a critical time-saver in Moldyn's approach.

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Molecular Simulation Inc. (MSI), one of Moldyn's subcontractors, performed testing of the simulations. As the testing proceeded, the researchers had difficulty identifying which substructures needed their degrees-of-freedom reduced. Sometimes the location of the active sites was unknown. Substructures were generated according to the variables entered, so great care had to be exercised in substructuring. Researchers had already discovered earlier in the project that if they over-constrained parts of the molecule design by using poor substructuring, then extreme instabilities in the substructures resulted. Consequently, as a general rule, project researchers assumed that if the substructures remained stable, then the variables entered into the program were reasonable, and it was more likely that drug candidate discoveries would be made.

Moldyn Uses a Team of Code Developers and Testers

The software developers at Moldyn worked with the following team of eight subcontractors, who contributed to various project tasks:

- Karplus and Associates validated the software code.
- Ornet Consulting Group served as a primary software developer. The group had previous experience as the primary developer for an all-atom software package already on the market.
- H.R. Research developed and tested the mode structures (variables) in the Moldyn software. There were several modes that controlled how molecule and drug interactions were simulated.
- MSI provided alpha and beta testing of the software at each stage of its development. MSI also was the product licensee. They provided the graphic user interface package called "Insight" that computed and constructed three-dimensional molecular models on a computer screen.
- Haney Associates performed research at MSI. Haney also provided customer support for the companies that purchased the software.
- Vertex Pharmaceuticals, Bristol Myers Squibb Pharmaceutical Research Institute, and Northeastern University served as alpha and beta testers.

Software Is Licensed and Field Tested

In the fall of 1997, near the end of the project, Moldyn signed a licensing agreement with MSI to sell and distribute its commercial software. Moldyn's software was bundled with MSI's computational chemistry software, Insight. The field test (beta) version of the bundled software was released in November 1997.

Moldyn Faces Obstacles in the MD Simulation Market

After the project ended, Moldyn was ready to start commercialization. The product was launched in 1998, with a time-to-market that was two to three years ahead of the company's competitors. Moldyn's 1999 sales were $100,000, but many of the products were returned due to customer dissatisfaction. The software was difficult to use and many of the simulations were unstable and, therefore, unusable. In retrospect, project principal investigators realized that if testers from MSI and other project subcontractors did not have an extensive knowledge of chemistry and physics, they were not able to enter sufficiently complete variable sets to generate stable substructures for the simulations. When unstable substructures occurred, the results of the simulation were unusable and invalid. Subsequently, new sales dropped as MD simulation

techniques fell out of favor with many customers. This was probably also due to the introduction of new technologies, such as combinatorial chemistry techniques that use “lab on a chip” and other arrays to quickly test target drug substances. These new methods were more efficient than MD simulation because they did not require extensive user knowledge. The “lab on a chip” and combinatorial chemistry approaches did work.

At the time of the final report for the project, Moldyn was pursuing more funding to finance refinements in molecular modeling with Small Business Innovation Research proposals, as well as internal funding. However, based on the difficulties encountered, neither Moldyn nor its parent, Photon Research Associates, had the additional funds required to enhance the MD simulation software that they had developed during the ATP-funded project. However, they did share their project research through 3 publications and 13 presentations.

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After the conclusion of the project, through a licensing agreement between Moldyn and Harvard University, Moldyn’s software was incorporated with Harvard's Chemistry at Harvard Macromolecular Mechanics (CHARMM) molecular modeling research software tool. CHARMM was originally developed in the early 1980s by project subcontractor Martin Karplus, and provided the molecular mechanics and dynamics framework for the Moldyn MD simulation software. As of 2004, CHARMM continues to be distributed by Harvard at no charge to academic and not-for-profit organizations for research purposes only. No intellectual property rights in either software package, the Moldyn software or CHARMM, were transferred in the Moldyn-Harvard licensing agreement.

In early 2000, Moldyn was acquired by Structural Bioinformatics Inc. (SBI), which subsequently changed its name to Cengent Therapeutics Incorporated in May 2003. According to the terms of the acquisition by SBI, the Moldyn software licensing agreement with Harvard was maintained.

Advent of New Technologies Causes Obsolescence of Molecular Dynamics Simulation

Moldyn’s software increased by a factor of 20 to 30 times the speed of simulating the all-atom model and achieved modeling accuracies of 10 to 20 percent or better in comparison to all-atom simulations. However, due to the program’s complexity and lack of predictability, consumers generally felt the program was undependable and not viable for commercial use. As of 2004, there was no customer interest in MD simulation software. The market for drug research had turned to high throughput screening techniques, including “lab on a chip” techniques that test for variables that flag new drug substances. Although it is very expensive for companies to set up high-throughput screening systems, as of 2004, all competitive drug research companies were using this technique.

Conclusion

Moldyn Inc. sought to improve molecular dynamics (MD) simulation software by modifying a fundamental task: substituting atom groups, called substructures, for many individual atoms in a molecule. The goal of the software was to virtually test the numerous potential drug substances to determine more quickly and at lower cost which ones were suitable as new commercial drug prospects. The most significant challenge in developing the software was to offer a faster but reasonably accurate molecular model that was superior to the all-atom model.

Although Moldyn made progress in several of the extremely complex tasks required to develop the software, the product failed. The primary reason for its failure was that the software users needed advanced knowledge in physics and chemistry, which the majority of the users lacked. Without this level of advanced expertise, the simulated models produced were unstable and therefore unusable. Consequently, the research community rejected the product. Despite the failure of the software, researchers learned much about the challenges of qualifying new drug agents for research. Moreover, they disseminated their knowledge through 3 publications and 13 presentations. As of 2004, MD simulation software is no longer used as a drug research technique; various high-throughput screening methods are now preferred.

PROJECT HIGHLIGHTS
Cengent Therapeutics Inc. (formerly Moldyn Inc.)

Project Title: Enhanced Molecular Dynamics Simulation for Drug Research (Enhanced Molecular Dynamics Simulation Technology for Biotechnology Applications)

Project: To develop a software that adapts a technology developed in the aerospace industry to simulations of biological molecule and drug interactions, for the purpose of qualifying drug research candidates in a more timely and efficient manner than by using trial-and-error techniques.

Duration: 2/15/1995 - 2/14/1998
ATP Number: 94-01-0137

Funding (in thousands):

ATP Final Cost	$1,988	60%
Participant Final Cost	1,341	40%
Total	$3,329	

Accomplishments: ATP funding enabled Moldyn to develop and test molecular dynamics (MD) simulation software. This type of software was of interest to the research community during a brief period in the mid-1990s. At that time, it provided some utility in helping experts better understand and characterize target proteins for drug research.

Commercialization Status: The MD simulation software was briefly commercialized through a license to Molecular Simulations Incorporated, but failed to gain sufficient sales and was discontinued. However, Moldyn's software was incorporated with Harvard's Chemistry at Harvard Macromolecular Mechanics (CHARMM) molecular modeling tool through a licensing agreement between Moldyn and Harvard Univesity.

Outlook: The outlook for this technology is poor. The software has been superceded by the use of high-throughput screening methods, which process vast numbers of possible new drug substances and select candidates that meet target variables.

Composite Performance Score: * *

Number of Employees: 7 at project start, 12 as of July 2004.

Company:

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Subcontractors:

- Bristol Myers Squibb Pharmaceutical Research Institute
  Princeton, NJ
- Haney Associates
  San Diego, CA
- H.R. Research
  Lawrenceville, NJ
- Karplus and Associates
  Cambridge, MA
- Molecular Simulation Inc.
  San Diego, CA
- Northeastern University
  Boston, MA
- Ornet Consulting Group
  Cambridge, MA
- Vertex Pharmaceuticals
  Cambridge, MA

Publications:

- Chin, D., K. Haney, H. Delak, C. Chun, and C. Padilla. "Nanosecond Simulations of the Unbinding Pathways of CBZ-Val-Phe-Phe-ValCBZ from the Active Site of HIV-1 Protease Using Multi-body Dynamics," *American Chemical Society Symposium Series on Rational Drug Design*, A. Parrill and R. Reddy, eds., 1998.
- Chin, D., K. Haney, H. Delak, H.M. Chun, and C.E. Padilla. "The Evaluation of Multi-Body Dynamics for Studying Ligand-Protein Interactions: Using MBO(N)D to Probe the Unbinding Pathways of Cbz-Val-Phe-Phe-Val-Cbz from the Active Site of HIV-1 Protease," *American Chemical Society Symposium Series 719, Rational Drug Design, Novel Methodology and Practical Applications*, A.L. Parrill, and M.R. Reddy, eds., p. 87-106, 2000.

PROJECT HIGHLIGHTS
Cengent Therapeutics Inc. (formerly Moldyn Inc.)

- Chun, H., C. Padilla, H. Alper, D. Chin, M. Watanabe, V. Karlov, K. Soosaar, K. Blair, O. Becker, L. Caves, R. Nagle, M. Karplus, and D. Haney. "MBO(N)D: A Multi-body Method of Long-time Molecular Dynamics Simulations," *Journal of Computational Chemistry,* 21:3, p. 159-184, 2000.

Presentations:

- Thacher, T. "Advances in the Accuracy and Utility of Protein Ligand Models, IBC Rational Drug Design - Computational Approaches to Analyze Protein Ligand Interaction/Binding Affinity," Dec. 11-12, 1995.
- Chun, H. "Substructured Modeling Approach for Large Macromolecules - MBO(N)D," MSI Potential Energy Functions Consortium Meeting, Rhone-Poulenc Rorer, Collegeville, PA, June 24-25, 1996.
- Padilla, C., H. Chun, O. Becker, L. Caves, and M. Karplus. "Substructured Modeling Approach for Macromolecules - MBO(N)D," Third Electronic Computational Chemistry Conference (ECCC-3), November 1996.
- Chun, H. MBO(N)D TV Demonstration, Presentation at MSI's exhibit booth at the American Chemical Society National Meeting, San Francisco, CA, April 13-15, 1997.
- Chun, H., D. Alper, M. Chin, K. Watanabe, C. Soosaar, O. Padilla, L. Becker, L. Caves, M. Karplus, and D. Haney. "MBO(N)D: A New Multibody Dynamics Methodology for the Modeling of Macromolecules as Substructures," American Chemical Society Meeting, San Francisco, CA, April 13-17, 1997.
- Chun, H.M., and C.E. Padilla. "New Techniques for Molecular Modeling and NMR Structure Determination and Refinement, Data Management for Drug Discovery and Design," IBC Conference, San Francisco, CA, June 23-24, 1997.
- Donovan, C. MBO(N)D presentations and demonstrations at MSI's exhibit booth at the Eleventh Symposium of the Protein Society, Boston, MA, July 12-16, 1997.
- Padilla, C., H. Alper, D. Chin, M. Watanabe, V. Karlov, K. Blair, K. Soosaar, H. Chun, O. Becker, L. Caves, R. Nagle, M. Karplus, and D. Haney. "Substructured Modeling Approach for Large Macromolecules - MBO(N)D," 36th IUPAC Congress, Geneva, Switzerland, August 17-22,1997.
- Chun, H., C. Padilla, V. Karlov, K. Blair, H. Alper, D. Chin, M. Watanabe, O. Becker, L. Caves, R. Nagle, M. Karplus, and D. Haney. "A Substructured Dynamics Method for Macromolecules - MBO(N)D. Part 1: Formulation and Methodology," 214th American Chemical Society National Meeting, Las Vegas, NV, September 7-11, 1997.
- Padilla, C., H. Alper, D. Chin, K. Soosaar, H. Chun, M. Watanabe, O. Becker, M. Karplus, and B. Farmer. "A Substructured Dynamics Method for Macromolecules - MBO(N)D. Part 2: Example Applications," 214th American Chemical Society National Meeting, Las Vegas, NV, September 7-11, 1997.
- Chin, D., C. Padilla, K. Delak, R. Czerminski, H. Alper, M. Watanabe, V. Karlov, R. Nagle, H. Chun, V. Mohan, and D. Haney. "Application of a Fast Computational Method for Studying Rupture Forces: HIV Ligand Interactions, and DNA Stretching," 214th American Chemical Society National Meeting, Las Vegas, NV, September 7-11, 1997.
- Chin, H., C. Padilla, K. Delak, R. Czerminski, H. Alper, M. Watanabe, V. Karlov, R. Nagle, H. Chun, V. Mohan, and D. Haney. "Studying Rupture Forces of HIV-Ligand Interactions, and DNA Stretching Using a Fast Computational Method," Poster paper, 214th American Chemical Society National Meeting, Las Vegas, NV, September 7-11, 1997.
- Chin, D., C. Padilla, H. Alper, M. Watanabe, V. Karlov, R. Czerminski, and H. Chun. "New Fast and Efficient Molecular Modeling Methods for Rational Drug Design: Structure-Based Design & Information Systems to Enhance Discovery Productivity," NMHCC Conference, Washington, D.C., September 11-12, 1997.